Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alkeran 2 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg melphalan.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off white, film-coated, round, biconvex tablets engraved 'GX-EH3' on one side and an 'A' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melphalan tablets are indicated in the treatment of:
- multiple myeloma;
- advanced ovarian adenocarcinoma.

Melphalan tablets may be used in the treatment of:
- breast carcinoma: melphalan either alone or in combination with other drugs has a significant therapeutic effect in a proportion of patients suffering from advanced breast carcinoma.

Alkeran Tablets may be used in the management of polycythaemia rubra vera.

4.2 Posology and method of administration

General
Alkeran is a cytotoxic drug which falls into the general class of alkylating agents. It should be prescribed only by physicians experienced in the management of malignant disease with such agents.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (see section 4.4).

Thromboembolic events
Melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism). Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see sections 4.4 and 4.8).
If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of melphalan treatment.

Posology

Multiple myeloma

A typical oral dosage schedule is 0.15 mg/kg bodyweight/day in divided doses for 4 days repeated at intervals of six weeks. Numerous regimens have, however, been used and the scientific literature should be consulted for details.

The administration of oral Alkeran and prednisone may be more effective than Alkeran alone. The combination is usually given on an intermittent basis.

Prolonging treatment beyond one year in responders does not appear to improve results.

Advanced ovarian adenocarcinoma

A typical regimen is 0.2 mg/kg bodyweight/day given orally in divided doses for 5 days. This is repeated every 4 to 8 weeks, or as soon as the bone marrow has recovered.

Carcinoma of the breast

Alkeran has been given orally at a dose of 0.15 mg/kg bodyweight or 6 mg/m2body surface area/day for 5 days and repeated every 6 weeks. The dose was decreased if bone marrow toxicity was observed.

Polycythaemia rubra vera

For remission induction doses of 6 to l0 mg daily for 5 to 7 days have been used, after which 2 to 4 mg daily were given until satisfactory disease control was achieved. A dose of 2 to 6 mg once per week has been used for maintenance therapy. In view of the possibility of severe myelosuppression if Alkeran is given on a continuous basis, it is essential that frequent blood counts are taken throughout therapy, with dosage adjustment or breaks in treatment, as appropriate, to maintain careful haematological control.

Paediatric population

Alkeran is only rarely indicated in the paediatric population and absolute dosage guidelines cannot be provided.

Older people

Although Alkeran is frequently used at conventional dosage in the older people, there is no specific information available relating to its administration to this patient sub-group. However, caution should be taken where there is renal impairment.

Renal impairment

Alkeran clearance, though variable, may be decreased in renal impairment (see section 4.4).

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering Alkeran Tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established.

Method of administration

Oral administration in adults: The absorption of Alkeran after oral administration is variable. Dosage may need to be cautiously increased until myelosuppression is seen, in order to ensure that potentially therapeutic levels have been reached.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Lactation.

4.4 Special warnings and precautions for use

ALKERAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised individuals. Therefore, immunisations with live organism vaccines are not recommended.

Monitoring

Bone marrow depression, with leucopenia and thrombocytopenia, is the main side effect. The time of maximum depression is variable, and careful attention should be paid to the monitoring of blood counts to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia.

Blood counts may continue to fall after treatment is stopped so at the first sign of an abnormally large fall in leukocyte or platelet counts treatment should be temporarily interrupted.

Alkeran should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

Venous thromboembolic events

Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of deep vein thrombosis and pulmonary embolism (see section 4.8). The risk appears to be greatest during the first 5 months of therapy, especially in patients with additional thrombotic risk factors (e.g. smoking, hypertension, hyperlipidaemia and history of thrombosis). These patients should be closely monitored and actions to minimize all modifiable risk factors should be undertaken. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. If a patient experiences any thromboembolic events, discontinue the treatment immediately and initiate the standard anticoagulation therapy. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy throughout the course of treatment.

Neutropenia and thrombocytopenia

Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving combination drug regimens described (section 4.8).

Mutagenicity

Melphalan has been shown to be mutagenic and carcinogenic in animals and chromosome aberrations have been observed in patients being treated with the drug. Melphalan has also been shown to be carcinogenic in animals (section 5.3), and the possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Carcinogenicity (Second primary malignancy)

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS)

Alkeran, in common with other alkylating agents has been reported to be leukaemogenic, especially in older patients after long combination therapy and radiotherapy.

There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloidosis, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and there has been a significant increase in patients with ovarian cancer.

A comparison of patients with ovarian cancer who received alkylating agents with those who did not showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia.

Before the start of the treatment, the leukaemogenic risk (AML and MDS) must be balanced against the potential therapeutic benefit, especially if the use of melphalan in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations may increase the leukaemogenic risk. Before, during and after treatment doctors must therefore examine the patient at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

Solid tumours
Use of alkylating agents has been linked with the development of second primary malignancy (SPM). In particular, melphalan in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone has been associated with the increased risk of solid SPM in elderly newly diagnosed multiple myeloma patients.

Patient characteristics (e.g. age, ethnicity), primary indication and treatment modalities (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g., tobacco use) should be evaluated prior to melphalan administration.

Contraception

Due to an increased risk of venous thromboembolism in patients undergoing treatment with melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, she should switch to another effective and reliable contraceptive method. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.
The recommended duration of contraception in females should be during treatment and for a period of six months following the cessation of treatment (see section 4.6).

Male patients should use effective and reliable contraceptive methods during treatment and for a period of three months following the cessation of treatment (see section 4.6).

Fertility

Male patients should have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of melphalan treatment (see section 4.6).
Renalimpairment

Alkeran clearance may be reduced in patients with renal impairment, who may also have uraemic bone marrow suppression. Dose reduction may therefore be necessary (see section 4.2), and these patients should be closely observed.

Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.
The use of high dose melphalan has the potential to cause acute kidney injury in patients, especially those with underlying renal impairment and potential risk factors for reduced renal function (e.g., concomitant use of nephrotoxic medications, amyloidosis etc).

4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in the paediatric population due to haemorrhagic enterocolitis.

In paediatric population, for the Busulfan-Melphalan regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Impaired renal function has been described in bone marrow transplant patients who were pre-conditioned with high dose intravenous melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Female patients should use effective and reliable contraceptive methods during treatment and for a period of six months, following the cessation of treatment.

Male patients should use effective and reliable contraceptive methods during treatment and for a period of three months following the cessation of treatment.
The final decision regarding the additional time period on contraception should be taken by the doctor and/or the patient (see section 4.4).

Pregnancy

There are no data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.
Alkeran should be not be used during pregnancy and particularly during the first trimester, unless considered absolutely essential by the physician. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving Alkeran.

Breast-feeding

Mothers receiving Alkeran should not breastfeed (see section 4.3).
Fertility

Alkeran causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

There is evidence from some animal studies that Alkeran can have an adverse effect on spermatogenesis (see section 5.3). Therefore, it is possible that Alkeran may cause temporary or permanent sterility in male patients.

It is recommended that men who are receiving treatment with melphalan have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of melphalan treatment. (see section 4.4).

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

4.8 Undesirable effects

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic agents.

The following convention has been utilised for the classification of frequency: Very common [3]1/10, common [3]1/100, <1/10, uncommon [3]1/1000 and <1/100, rare [3]1/10,000 and <1/1000, very rare <1/10,000, not known (cannot be estimated from the available data).

Body System	**Frequency**	**Side Effects**

Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	secondary acute myeloid leukaemia and myelodysplastic syndrome (see section 4.4).
Blood and Lymphatic System Disorders	Very common	bone marrow depression leading to leucopenia, thrombocytopenia, neutropenia[1] and anaemia.
	Rare	haemolytic anaemia.
Immune System Disorders	Rare	hypersensitivity[2] (see Skin and Subcutaneous Tissue Disorders).
Respiratory, Thoracic and Mediastinal Disorders	Rare	interstitial lung disease and pulmonary fibrosis (including fatal reports).
Gastrointestinal Disorders	Very common	nausea[3], vomiting[3] and diarrhoea; stomatitis at high dose.
	Rare	stomatitis at conventional dose.
Hepatobiliary Disorders	Rare	liver disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice.
Skin and Subcutaneous Tissue Disorders	Very Common	alopecia at high dose.
	Common	alopecia at conventional dose.
	Rare	rash maculo-papular and pruritus (see Immune System Disorders).
Renal and Urinary Disorders	Common	blood urea increased[4]
	Not known	Acute kidney injury
Vascular Disorders[5]	Not known	deep vein thrombosis and pulmonary embolism
Reproductive system and breast disorders	Not known	azoospermia, amenorrhoea.
General Disorders and Administration Site Conditions	Very common	pyrexia

1. Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone (see sections 4.4)
2. Allergic reactions to melphalan such as urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Cardiac arrest has also been reported rarely in association with such events.
3. Gastrointestinal effects such as nausea and vomiting have been reported in up to 30% of patients receiving conventional oral doses of melphalan.
4. Temporary significant elevation of the blood urea has been commonly seen in the early stages of melphalan therapy in myeloma patients with renal damage.
5. The clinically important adverse reactions associated with the use of melphalan in combination with thalidomide and prednisone or dexamethasone and to a lesser extend melphalan with lenalidomide and prednisone include: deep vein thrombosis and pulmonary embolism (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms and signs

Gastro-intestinal effects, including nausea, vomiting and diarrhoea are the most likely early signs of acute oral overdosage. The principal toxic effect is bone marrow suppression, leading to leucopoenia, thrombocytopenia and anaemia.

Treatment

General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation cover with anti-infective agents, and the use of haematological growth factors.

There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdosage until there is evidence of recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues, ATC code: L01AA03.

Mechanism of action
Melphalan is a bifunctional alkylating anti-neoplastic agent with some immunosuppressant properties. Formation of carbonium intermediates from each of the two bis- 2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication.

5.2 Pharmacokinetic properties

Absorption

The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the drug in plasma and peak plasma concentration.
In studies of the absolute bioavailability of melphalan the mean absolute bioavailability ranged from 56 to 85%.
Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.

In a study of 18 patients administered melphalan 0.2 to 0.25 mg/kg bodyweight orally, a maximum plasma concentration (range 87 to 350 nanograms/ml) was reached within 0.5 to 2.0 h.
The administration of melphalan tablets immediately after food delayed the time to achieving peak plasma concentrations and reduced the area under the plasma concentration-time curves by between 39 and 54%.

Distribution

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in paediatrics.

Elimination

In 13 patients given oral melphalan at 0.6 mg/kg bodyweight, the plasma mean terminal elimination half-life was 90 57 min with 11% of the drug being recovered in the urine over 24 h.
In 18 patients administered melphalan 0.2 to 0.25 mg/kg bodyweight orally , the mean elimination half -life was 1.12 ± 0.15 h.

Special PatientPopulations

Renal impairment

Melphalan clearance may be decreased in renal impairment (see section 4.2 and 4.4).

Elderly
No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2).

5.3 Preclinical safety data

Mutagenicity
Melphalan is mutagenic in animals.

Reproductive toxicity
Reproduction studies in rats treated with oral doses of 0.81-2.42 times the Maximum Recommended Human Dose (MRHD) revealed embryolethal and teratogenic effects. Congenital anomalies included those of the brain (underdevelopment, deformation, meningocele, and encephalocele), eye (anophthalmia and micropthalmos), reduction of the mandible and tail, and hepatocele (see section 4.6).

Fertility Studies
In mice, melphalan at clinically relevant exposure levels showed reproductive effects attributable to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-meiotic germ cells, particularly in mid to late stage spermatids.

Females received melphalan at clinically relevant exposure levelsand were then housed with an untreated male for most of their reproductive life span. A pronounced reduction in litter size occurred within the first post-treatment interval, followed by an almost complete recovery. Thereafter, a gradual decline in litter size occurred. This was simultaneous with a reduction in the proportion of productive females, a finding associated with an induced reduction in the number of small follicles (see section 4.6).

Genotoxicity
Melphalan has been tested for genotoxicity in a number of short-term assays, both *in vitro* and *in vivo*.
In mice, oral administration of melphalan at a dose of 0.81 times the MRHD increased frequencies of dominant lethal mutations, chromosomal aberrations, sister chromatic exchange, micronuclei and DNA strand breaks.
The observed mutations originated primarily from large deletions in the postspermatogonial cells whereas other types of mutagenic mechanisms predominated in the spermatogonial cells.
This *in vivo* data is supported by *in vitro* studies showing that cell culture treatment with melphalan (at concentrations ranging from 0.1 to 25 µM) also induced DNA damage.
In addition, it induced aneuploidy and sex-linked recessive lethal mutations in Drosophila, and mutation in bacteria. It was positive with all strains in the Ames test at concentrations of 200 µg/plate and above. The mutagenic activity of melphalan was increased 3-fold in the presence of liver S9 metabolising preparations, which is unexpected since melphalan is not considered to need liver activation to produce a cytotoxic effect.

Carcinogenicity
Melphalan is a direct-acting alkylating agent that is carcinogenic via a genotoxic mechanism, which is sufficiently supported by animal studies.
Development of neoplastic tumours in mice reported following oral administration of melphalan at doses of 0.10-1.63 times the MRHD; in monkeys, the carcinogenic potential was observed at a dose of 0.16 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Microcrystalline cellulose
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Tablet film-coating
Hypromellose
Titanium Dioxide
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator 2°C to 8°C.

6.5 Nature and contents of container

Alkeran Tablets are supplied in amber glass bottles of 25 or 50 tablets with a child-resistant closure.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The handling of Alkeran formulations should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations.

Pregnant Staff should not handle cytotoxics.

Protective clothing, including gloves, should be worn.

Alkeran Tablets should not be divided.

Provided the outer coating of the tablet is intact, there is no risk in handling Alkeran Tablets.

Disposal
Alkeran Tablets should be destroyed in accordance with relevant local regulatory requirements concerning the disposal of cytotoxic drugs.

Adequate care should be taken in the disposal of waste material, including containers and any other contaminated material.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/004/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

January 2025